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RESEARCH**

APPLICATION NUMBER:

22-026

APPROVABLE LETTER



NDA 22-026

Synthon Pharmaceuticals, Inc.
Attention: Michael Hinckle
9000 Development Drive
P.O. Box 110487
Research Triangle Park, North Carolina 27709

Dear Mr. Hinckle:

Please refer to your January 31, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for amlodipine besylate 2.5, 5 and 10 mg Orally Disintegrating Tablets.

We acknowledge receipt of your submissions dated March 20, June 8, and October 17, 2006.

We have completed our review of this application, as amended, and it is approvable.

Before the application may be approved, it will be necessary for you to address the following comments:

1. Submit information to address the difference in T_{max}. A significant difference was observed for T_{max} between the TEST and the REFERENCE treatments according to Wilcoxon and median non-parametric tests and ANOVA. The mean of T_{max} was 11.09 hours (6 hours – 32 hours) for the TEST formulation and 7.17 hours (4 hours – 12 hours) for the REFERENCE formulation.
2. The waiver requested for the lower strengths, 2.5-mg and 5.0-mg strength orally disintegrating tablets (ODTs), is not granted. Please submit additional dissolution data to support the biowaiver requested. Dissolution data should be obtained on a minimum of 12 individual units of each strength, 2.5-mg and 5-mg ODTs, and compared to the 10 mg ODT biolot. The proposed dissolution method can be used with three media covering the physiological pH range (i.e.; pH 1.2, 4.5 and 6.8). The information using 0.01N HCl submitted with the current application can be substituted for the pH 1.2 medium. Samples should be collected at a sufficient number of intervals to characterize the dissolution profile of the drug product. Individual data, mean percent dissolved, range (highest and lowest) of dissolution, and coefficient of variation (relative standard deviation) should be tabulated. A graphic representation of the mean dissolution profiles for the test and reference products in the three media should also be included. Similarity in dissolution profiles between the test and reference products in each of the three media, using the f₂ metric, should be determined.
3. After evaluation of the dissolution data submitted, the dissolution specification should be tightened. The following dissolution method and specification is recommended:

USP Apparatus 2: Paddle Method
Rotation speed: 50 rpm
Volume: 500 mL
Medium: 0.01 M HCl
Tolerance: Q — in 15 minutes

b(4)

4. Please submit available dissolution data at a 15 minute time point from current primary stability batches.
5. Revise the stability protocol for the primary stability batches to include a 15 minute time point and all future data should be collected and reported accordingly.
6. The FDA inspections revealed significant deficiencies in the documentation and procedural aspects of your bioequivalence studies conducted at _____ . The primary concern is a lack of documentation, to verify at the time of dosing, the treatment received by each subject. Satisfactory resolution of these deficiencies is required before this application may be approved. Therefore it will be necessary for you to repeat a study at _____ to demonstrate that, with proper documentation and procedures, the results of an earlier study can be reproduced. It is suggested that you conduct a bioequivalence study of the amlodipine besylate orally disintegrating 10 mg tablet vs. Pfizer's Norvasc 10 mg tablets in 26 subjects. The acceptance criteria for a study are outlined below.

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Criteria for Acceptance of Synthon's Repeat Amlodipine Study

The repeat amlodipine study [comparing Synthon's 10 mg amlodipine orally disintegrating tablets (ODT) versus Pfizer's NORVASC® 10 mg tablets] to be conducted at _____ should satisfy the following criteria:

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- The repeat study must have adequate documentation of the drug products that addresses the FDA audit findings for shipment, receipt, storage, dispensing, and administration of drugs, and blood collection to assure that subjects received the intended product on each occasion.
- It is recommended that the number and gender distribution of subjects be similar to that of the original study (i.e., 13 males and 13 females), and the age distribution should be similar (18-55 years).
- The repeat study outcome should meet similar bioequivalence criteria (i.e., 90% confidence intervals for AUC_{0-t} , AUC_{0-inf} and C_{max} within 80-125%) as the original study.

~~The point estimates for AUC_{0-t} , AUC_{0-inf} and C_{max} for the two studies should be within 15%.~~

- Any pharmacokinetic (PK) repeats are subject to the same PK repeat criteria established for the original study's SOP. If there was no SOP with such criteria for the original study, then no PK repeats can be performed for the new study.
- The study records, both clinical and analytical, may be subject to FDA inspection. Reserve samples of the drug products, selected at _____ from the products supplied to them, must be available for collection by FDA or for submission to FDA upon request.

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The Agency shall provide relief to you by removing the adverse inspectional findings from the amlodipine besylate orally disintegrating tablets if it is determined that the new study meets the predefined criteria. This information from the repeat study will provide the Agency with the minimal assurance that the data from your bioequivalence studies conducted at _____ are accurate and valid.

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Given the extent of the additional information needed, final labeling cannot be considered at this time. If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling will be required.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please call Commander Denise M. Hinton, Regulatory Project Manager, at (301) 796-1090.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Norman Stockbridge
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